Remarks

Claims 1 to 21 were in the application as filed. Claims 1 to 21 were cancelled and Claims 22 to 33 were added in the Preliminary Amendment filed on September 10, 2003. Claim 30 was cancelled and claims 34 to 36 were added in the Amendment filed on June 26, 2007. Claims 23, 28, and 29 were cancelled in the Amendment filed on September 14, 2007.

The title has been amended to reflect that the invention is directed to quinoline derivatives.

Claim 34 has been amended to more clearly indicate that the claim is directed to a combination therapy and not to a pharmaceutical composition.

Claim 35 has been amended to comport said claim with conventional U.S. Markush claim format. Claim 35 has also been amended to further specify the other anticancer compounds.

No new matter has been added by these amendments.

Claims 22, 24 to 27, and 31 to 36 are currently pending in this application.

Applicants acknowledge, with appreciation, the Examiner's statement that the rejection under 35 U.S.C. § 112, first paragraph, of claims 26, 28 to 29 and 31 to 36 "regarding the treatment of all forms of cancer has been overcome," and that the rejection under 35 U.S.C § 112, first paragraph "regarding a method of using compounds of formula I with radiation has been overcome" (Office Action, page 2).

Applicants further acknowledge, with appreciation, the Examiner's allowance of claims 25, 26 and 36. It is believed that claim 33 is also considered allowable, as no pending rejections pertain to said claim.

Discussion of Telephonic Interview

The telephone interviews of November 6, 2007 and November 8, 2007, between Examiner Noble Jarrell and Applicants' undersigned representative are gratefully acknowledged.

A copy of a proposed amendment to claim 34 was sent via facsimile to Examiner Jarrell on November 6, 2007. The Examiner stated that the proposed amendment to claim 34 would overcome the enablement rejection of said claim regarding the "stable compositions of

compounds of formula I and anticancer agents." Applicants have therefore amended Claim 34 as previously proposed.

The Examiner also suggested cancelling the terms "oestrogenic hormones" and "androgenic hormone," and using conventional Markush claim formatting for claim 35. Applicants have amended claim 35 according to these suggestions.

The pending rejection of claims 22 and 27 under 35 U.S.C. § 103(a) and the pending, provisional rejection of claims 22, 24, and 27 on the grounds of obviousness type double patenting were not discussed.

Discussion of Foreign Priority

It is noted that Applicants' claims of foreign priority to French Patent Application Nos. FR 99 15031, filed November 29, 1999, and to FR 00 10561, filed August 11, 2000 have not been acknowledged.

Applicants call the Examiner's attention to parent Patent Application No. 09/722,361 (now U.S. Patent No. 6,645,964) wherein certified copies of FR 99 15031 and FR 00 10561 were filed. According to MPEP 201.14(b)(II):

> Where the benefit of a foreign filing date based on a foreign application is claimed in a later filed application (i.e., a continuation, continuation-in-part, division) or in a reissue application and a certified copy of the foreign application as filed, has been filed in a parent or related application, it is not necessary to file an additional certified copy in the later application.

Acknowledgement of these documents and of Applicants' claims to priority of FR 99 15031 and FR 00 10561 is respectfully requested.

Objection to the Specification

The Examiner maintains that the title of the invention is unclear and has required a new title "that is clearly indicative of the invention to which the claims are directed." (Office Action, page 2).

This objection is believed overcome and should be withdrawn in view of the above-described amendment to the title, as required by the Examiner.

Discussion of Rejection under 35 USC § 112, First Paragraph

The Examiner has maintained the rejection of claims 31, 32, 34, and 35 under 35 U.S.C. § 112, first paragraph, "regarding compositions of compounds of claim 1 with other anticancer agents." The Examiner states that "Applicants have still not shown that stable compositions can be formed with compounds of formula I and anticancer agents" (Office Action, page 2).

Applicants again respectfully submit that the rejected claims are method of treatment claims directed to a combination therapy and not to pharmaceutical compositions, as the Examiner states. "Combination" does not equate to "composition". However, in order to progress this present application, Applicants have amended claim 34 to remove the word "combination". Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Discussion of Rejection under 35 U.S.C. § 103(a)

Claims 22 and 27 are *newly* rejected under 35 U.S.C. § 103(a) as being, the Examiner alleges, unpatentable over Singh et al. (*Journal of Medicinal Chemistry*, 1971, 14(6), 532-535), in view of Patani and LaVoie (*Chemical Reviews*, 1996, 96, 3147-3176) and Evans et al. (*Journal of Medicinal Chemistry*, 1967, 10, 428-31). The Examiner maintains that "Singh et al. teach structure 22 of table 1, which does not anticipate formula I because both quinoline rings each have one chlorine attached to them," and that "Patani and LaVoie teach on page 3153, table 12, that a Cl atom is a bioisosteric equivalent group for H." (Office Action, page 3).

This rejection is traversed and reconsideration and withdrawal thereof are respectfully requested for the reasons given hereinbelow.

The primary reference cited by the Examiner, Singh et al., teaches a structure 22 having particular chlorine substitution not present on Applicants' claimed compounds. Recognizing this deficiency of the primary Singh reference, the Examiner relies on Table 12 of Patani and LaVoie for an alleged teaching of "bioequivalence" between a chlorine atom and a hydrogen atom. However, the results provided by Patani and LaVoie clearly indicate the opposite: replacing a chlorine atom with a hydrogen atom changed the activity of the particular molecule significantly

("Within this series, it was observed that hydrogen bond donors were more potent than the unsubstituted parent compound. ...Thus, at the 9-position, *optimal size* and lipophilicity appear to be ***critical factors*** associated with their ability to inhibit thymidylate synthase," Patani and LaVoie at 3153, emphasis added). Based on this disclosure, one skilled in the art would not have a reasonable expectation of success that replacing a chlorine atom with a hydrogen atom would provide a molecule of similar activity given the well know size difference between a chlorine atom and a hydrogen atom.

The third reference, Evans et al., is cited for allegedly teaching a pharmaceutically acceptable composition. The Examiner argues that "[t]ested compounds were mixed with **carageenan** [sic] and saline **for injection**...Since this composition was given orally to rats, the composition can be considered pharmaceutically acceptable." (Office Action, page 3, emphasis added).

According to Evans et al., "carrageenin is a phlogistic agent" (p. 429, column 1), i.e. it causes inflammation. Although Evans et al. may have orally administered anti-inflammatory agents to rats, the carrageenin solutions were injected into the rats in order to *cause* inflammation. Nothing in Evans et al. would lead one skilled in the art to consider a carrageenin solution "pharmaceutically acceptable."

The Examiner further maintains that "Singh et al. used the same composition in their paper...Singh made a composition of compounds 22, carageenan, [sic], and saline, which was given to rats" (Office Action, page 4). Applicants disagree. The article referenced by Singh et al. was Osdene et al. (*Journal of Medicinal Chemistry*, 10, **431** (1967)), which relates to antimalarials, and not Evans et al. (*Journal of Medicinal Chemistry*, 10, **428** (1967)), which relates to antiinflammatories. The Evans et al. article is simply adjacent to the Osdene article in the same journal. Applicants respectfully submit that the Evans et al. article was cited in error.

For the reasons set forth above, Singh et al., Patani and LaVoie, and Evans et al., taken either individually or in combination, are incompetent to render Applicants' claimed compounds obvious. Therefore, the rejection of claims 22 and 27 under 35 U.S.C. §103(a) based on said references is believed to be unwarranted and should be withdrawn.

Discussion of Double Patenting Rejection

The Examiner has *newly* provisionally rejected claims 22, 24, and 27 on the grounds of non-statutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 3, 5, and 9 of copending Application No. 10/996,637.

As this is only a provisional double-patenting rejection, Applicants will wait until this double patenting rejection is the sole remaining issue in the instant application or U.S. Patent Application No. 10/996,637, and at that time Applicants will address the obviousness-type double patenting issue.

There being no remaining issues, this application is believed in condition for favorable reconsideration and early allowance, and such actions are earnestly solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,

November 19, 2007
Date

Kelly L. Bender, Reg. No. 52,610
Attorney for Applicants

sanofi-aventis U.S. Inc.
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
Bridgewater, NJ 08807-0800
Telephone (610) 889-8995
Telefax (908) 231-2626

sanofi-aventis Docket No. ST99049G1 US DIV